Association between mean systolic and diastolic blood pressure throughout the follow-up and cardiovascular events in acute myocardial infarction patients with systolic dysfunction and/or heart failure: an analysis from the High-Risk Myocardial Infarction database initiative

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.1131

Abstract

Background: Observational data have described the association of blood pressure (BP) with mortality as a "J" shaped i.e. mortality rates increase below a certain BP threshold. We aimed to analyze the associations between BP and prognosis in a population of acute myocardial infarction (MI) patients with heart failure (HF) and/or systolic dysfunction.

Methods: The datasets included in this pooling initiative are derived from four trials: CAPRICORN, EPHESUS, OPTIMAAL and VALIANT. A total of 28,771 patients were included in this analysis. Arithmetic mean of all office BP values measured throughout follow-up were used. The primary outcome was cardiovascular death.

Results: The mean±SD age was 65±11.5 and 30% were female. Patients in the lower systolic blood pressure (SBP) quintiles had higher rates of cardiovascular death: adjusted HR (95%CI)=2.49 (2.26-2.74) for SBPd112 mmHg and HR (95%CI)=1.29 (1.16-1.43) for SBP between 113 and 120 mmHg (reference: SBP=121 to 128 mmHg). The findings for HF hospitalization and MI were similar. However, stroke rates were higher in patients within the highest SBP quintile (reference: SBP=121 to 128 mmHg): HR (95%CI)=1.38 (1.11-1.72). Patients who died had a much shorter follow-up (0.7 vs. 2.1 years), less BP measurements (4.6 vs. 9.8) and lower mean BP (-8 mmHg in the last SBP measurement compared to patients who remained alive during the follow-up), suggesting that the associations of low BP and increased cardiovascular death represent a reverse causality phenomenon.

Conclusion: SBP values below 125 mmHg were associated with increased cardiovascular death, but these findings likely represent a reverse causality phenomenon.

Key-words: blood pressure; myocardial infarction; heart failure; cardiovascular outcomes.

Introduction

Although is undisputable that lowering blood pressure improves outcome of hypertensive patients[1], the threshold to which blood pressure should be lowered is a matter of debate and likely to be population-specific[2-4]. In addition, several observational studies and post-hoc analyses have suggested that lowering blood pressure below a certain threshold may be deleterious, as reflected by the so-called J-curve phenomenon[5-7]. An observational study in 22,672 "real-life" patients with stable coronary artery disease treated for hypertension, a low systolic (<120 mm Hg) and diastolic (<70 mm Hg) blood pressures were associated with an increased risk of cardiovascular events, supporting the J-curve phenomenon, and suggesting that in patients with coronary artery disease a low blood pressure may be deleterious[8].

Recently the SPRINT trial showed that assigning high cardiovascular risk patients (but without diabetes or prior stroke) to an intensive blood pressure (BP) treatment arm with the goal of lowering systolic blood pressure (SBP) below 120 mmHg versus a standard treatment arm with the goal of lowering SBP below 140 mmHg, improved outcomes in this population, notably by reducing the rates of heart failure (HF) hospitalizations and death (both cardiovascular and all-cause)[9]. The SPRINT trial results were also reinforced by a recent meta-analysis of trials allocating patients in intensive versus standard treatment arms[10], although in this meta-analysis the mean BP in the intensive therapy group was 133/76 mmHg, compared to 140/81 mmHg in the standard therapy group. Therefore, a discrepancy exists between data derived from randomized trials and data derived from observational studies. One potential explanation is that observational data are prone to bias, notably residual confounding and reverse causality. This last is particularly relevant, i.e. is not lower blood pressure that causes

the adverse outcomes, but instead are the "sicker" patients who have lower blood pressure near their life-end[11].

The aim of the present manuscript is to study the association between blood pressure levels and cardiovascular outcomes in a large cohort of acute myocardial infarction patients with systolic dysfunction and/or HF.

Methods

Study population

The high-risk MI initiative consists of a previously published cohort of pooled patient data derived from four clinical trials[12]. Briefly, the main objectives of the project are to provide a comprehensive and statistically robust analysis of long-term clinical outcomes in high-risk survivors of MI. The datasets included in this pooling initiative were: the effect of Carvedilol on Outcome after Myocardial Infarction in Patients with Left Ventricular Dysfunction trial (CAPRICORN)[13, 14], the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[15, 16], the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL)[17, 18] and the Valsartan in Acute Myocardial Infarction trial (VALIANT)[19, 20]. Full details of total enrolled patients, the inclusion and exclusion criteria for each trial, the endpoints as well as the results have previously been published[12]. Each trial enrolled patients with left ventricular systolic dysfunction, HF or both between 12 h and 21 days after acute MI.

The respective chairpersons of the Steering Committees of the four trials initiated the pooling project.

The studies were all conducted in accordance with the Declaration of Helsinki and approved by site ethics committees. All participants gave written informed consent to participate in the studies.

Blood pressure measurements

In each trial, the investigators measured patients` office blood pressure after a rest of 5 minutes in the sitting position at each ±4-month interval using an automated electronic sphygmomanometer. Three BP measurements were performed at each visit and the mean BP at each visit was used in the present study. The main analysis was done with the arithmetic mean of all blood pressure values measured throughout follow-up, from the baseline visit to the visit before an event or (in patients without an event) up to the last visit. All analyses were done for

systolic blood pressure and diastolic blood pressure separately (Pearson correlation SBP/DBP =0.67). Patients were categorised into five groups (i.e., balanced quintiles) for both systolic and diastolic blood pressure.

Outcomes

The primary outcome was cardiovascular death. Secondary outcomes were hospitalization for heart failure, myocardial infarction, stroke, and all-cause death.

We only analysed patients with at least one BP measurement before the outcome. Endpoints were independently adjudicated in the respective trials.

Statistical methods

In descriptive analyses, continuous variables are expressed as mean ± standard deviation (SD) as they were normally distributed. Categorical variables are expressed as frequencies and proportions (%).

The one-way analysis of variance "ANOVA test" was used to compare blood pressure across quintiles. Baseline laboratory measurements were obtained at the time of inclusion. The estimated glomerular filtration rate was calculated using the CKD-EPI equation[21]

Cox proportional hazard regression models were used to model the associations between blood pressure and long-term events both in univariable and multivariable analysis. Cox model assumptions were verified and blood pressure measurements were analysed as quintiles and also converted to restricted cubic splines as association with outcomes was non-linear. In the multivariable models, the covariates were chosen from demographic (age and gender), clinical (body mass index, smoking, hypertension, diabetes, heart failure history, previous stroke, previous myocardial infarction, peripheral artery disease, atrial fibrillation and heart rate), laboratorial (estimated glomerular filtration rate), and concomitant treatments (ACEi/ARBs, beta-blockers, and diuretics). All variables were previously found to be clinically relevant and associated with outcomes[22]. An interaction term between blood pressure measures and age was prespecified in the statistical analysis plan and was non-significant for all outcomes ($p > 0.1$). No multiple imputation was performed and only variables with <10% of missing values were used for adjustment. Left ventricular ejection fraction, glucose, electrolytes and hemoglobin were not included for adjustment in the models` due to a high (>75%) percentage of missing values.

Model calibration was assessed visually by plotting the mean of model-predicted survival at 2 years in each decile of predicted survival against the observed survival estimated

by the Kaplan-Meier method as previously described[23].

Statistical analyses were performed using the R software (The R Foundation for Statistical Computing). A p value <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 28,771 patients were included in the present analysis (no patients were excluded). The mean ± standard deviation age was 65 ± 11.5 years and 30% were female. The overall mean follow-up was 2.0 ± 1.0 years (2.1 ± 0.8 years in the group of patients who remained alive during follow-up vs. 0.7 ± 0.6 years in those who died from CV causes).

By quintiles of SBP, patients in the lower quintiles were younger, more often male, active smokers, with history previous myocardial infarction, and had lower body mass index, lower left ventricular ejection fraction, lower serum sodium levels, higher heart rate and better eGFR (all p<0.0001). **Table 1**. Patients in the lower quintiles of DBP were older, more often diabetic, and with worse renal function, but they also had lower ejection fraction, body mass index, and serum sodium, were more often smokers, and had previous myocardial infarction more often reported, as described for SBP. **Supplemental Table 1**.

Mean blood pressure outcome associations

Patients in the lower quintiles of SBP had higher rates of cardiovascular death compared to patients with a SBP between 121 and 128 mmHg (reference category): adjusted hazard ratio (HR), 95% confidence interval (CI) =2.49 (2.26-2.74) for SBP d112 mmHg and 1.29 (1.16-1.43) for SBP between 113 and 120 mmHg. **Table 2**. Patients in the higher SBP quintile had the lower rate of cardiovascular death, adjusted HR (95%CI) =0.76 (0.68-0.85) for SBP >137 mmHg, compared with the same reference group. Consistent findings were also observed for HF hospitalization and myocardial infarction. **Table 2**. Regarding stroke, patients in the higher and lower mean SBP quintile had a higher stroke risk: HR (95%CI) =1.38 (1.11-1.72) and 1.66 (1.32-2.10), respectively (compared with the reference group of SBP between 121 and 128 mmHg). **Table 2**. Patients in the lowest quintiles of DBP also presented increased risk of cardiovascular death, adjusted HR (95%CI) =1.88 (1.70-2.07) for DBP d68 mmHg and HR (95%CI) =1.23 (1.10-1.36) for DBP of 69 to 72 mmHg. High DBP was also independently associated with increased stroke rate, HR (95%CI) =1.41 (1.13-1.75). **Supplemental Table 2**. Sensitivity analysis excluding patients with diabetes, stroke history and eGFR <45

ml/min/1.73m2 and additional adjustment for each trial and oral anticoagulant use, provided similar results to those observed in the whole population. **Supplemental Table 3 & 4.** Restricted cubic spline graphical representations of the relationship between BP and the outcomes of interest are depicted in **Figure 1**.

Blood pressure analysis and comparison of patients with and without events

Compared to those who were alive, patients who died from cardiovascular causes during the follow-up had similar absolute BP values at baseline (i.e. randomization): 121/72 mmHg (alive) vs. 122/72 mmHg (dead), but lower BP before the fatal event: 129/76 mmHg (alive) vs. 121/72 (dead); absolute difference in SBP = +1 mmHg in those who died at baseline vs. -8 mmHg in those who died in the last available recording. Patients who died from cardiovascular causes also had fewer BP measurements during the follow-up (5 vs. 10 measures) and a much shorter mean follow-up (0.7 vs. 2.1 years). Consistently, in the patients who died during follow-up, the mean BP was lower than in patients who remained alive. **Table 3**. Patients with non-fatal events (HFH, MI, stroke) also had fewer BP measurements (~~H~~4 vs. 9) and a much shorter follow-up (0.7 vs. 1.9 years) compared to patients with fatal events. Patients with HFH and MI also presented lower last BP values compared to patients who did not have these events (128/76 vs. 123/73 for HFH and 128/76 vs. 125/73 for MI). On the other hand, patients who had a stroke had higher last BP values compared to patients without stroke events (127/75 vs. 129/76). **Supplemental Table 5**. The associations between baseline (i.e. randomization) BP values and last (i.e. before cardiovascular death or last available if alive) BP values are represented graphically in the **Supplemental Figures 1 to 5**.

Discussion

The results of the present study in a specific population of patients with systolic dysfunction or overt HF after MI, show that blood pressure levels below 125/75 mmHg are associated with worse outcomes. The so-called J-shaped phenomenon (i.e. a higher cardiovascular risk below a certain BP threshold) was also observed in this large dataset. However, we found that patients with a fatal event had fewer BP measurements and lower last BP values compared to patients who remained alive during follow-up. Therefore, their mean BP approached the end-life values, suggesting a reverse causation as explanation for these findings.

In our study patients with lower mean BP were also those with higher heart rate, lower body mass index (BMI), with higher proportion of previous MI, and current smoking. All these

variables have been associated to worse outcomes in patients with HF and/or MI[24-27] and are likely to carry residual confounding, accounting, in part, for the reported associations. In the present manuscript, after adjusting for potential confounders, having a low systolic (<125 mmHg) and diastolic (<75 mmHg) BP was associated with non-fatal cardiovascular events (MI, stroke, HF hospitalization) and also death (both cardiovascular and from all-causes). Overlapping results were observed in a subpopulation with less co-morbidities (i.e., no diabetes, no previous history of stroke and with eGFR >45 ml/min/1.73m^2). Interestingly, in this population having high SBP (>140 mmHg) was only independently associated with a higher risk of stroke (but not CV death, MI or HF hospitalization). Patients who had a stroke were the only population with a non-fatal event that had higher blood pressure values before the event. These findings (positive association of low BP with all CV events and high BP only with stroke) may support the theoretical notion that patients with CAD may require higher BP levels to maintain coronary perfusion[8]. However, in SPRINT[9], the intensive treatment benefit was present regardless of the presence of previous cardiovascular disease (p for interaction =0.39) and the attained mean BP levels in the intensive treatment group were 121.4/68.7 mmHg vs. 136.2/76.3 mmHg in the standard treatment group. The ACCORD[2] trial enrolled diabetic patients at high cardiovascular risk and also targeted SBP of less than 120 mmHg. However, in the ACCORD trial intensive treatment did not reduce the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, but it reduced the prespecified secondary outcome of annual rates of stroke (although the ACCORD trial might have been underpowered to detect between group differences for the primary outcome as it had half of the sample size of SPRINT and did not incorporate HF hospitalizations in the primary outcome). In the HOPE-3 trial, blood pressure lowering in intermediate risk persons without cardiovascular disease also did not reduce the coprimary composite outcome of CV death, MI or stroke, but the prespecified subgroup of patients with baseline SBP >143.5 mmHg seemed to benefit from anti-hypertensive therapy[28]. Despite patients included in the HOPE-3 trial represent a completely different setting from those studied herein, no event rate increase was observed in patients with lower baseline BP. On the other hand, in observational studies the association with adverse prognosis steeply increases with BP levels below 125/75 mmHg (like in the present study)[4, 5, 8, 29], however (in addition to potential residual confounding bias, as above referred) one should account for reverse causation bias. In a post-hoc analysis derived from the ONTARGET and TRANSCEND trials[29] - that tested the

efficacy and safety of ARBs on high CV risk populations - the authors found a "J-shaped association" of SBP and DBP with CV death, MI, and HF (but not stroke). Nonetheless, the authors also state that they cannot rule out a reverse causality effect on their findings, as multiple co-morbidities may cause BP decrease and are associated with higher morbidity and mortality rates during the trial. The present analysis, demonstrates that patients who died had lower BP values compared to those who remained alive during follow-up (despite similar mean BP values at baseline). A recent population-based study also showed a lower mean BP values in patients who died, suggesting that nonrandomized epidemiological associations of low SBP with higher mortality may be due to reverse causation, because participants with lower blood pressure values are closer, on average, to the end of life[30]. These findings suggest that a reverse causation bias is likely to drive the present associations as patients approaching death have lower BP values, which may be due to poor health conditions (e.g. "pump" failure, systemic inflammation, renal disease) and deteriorating nutritional status toward the end of life[31, 32]. Therefore, one should be very cautious in mixing apples and oranges, as data from randomized controlled trials (RCTs) provide much stronger evidence than observational or retrospective analysis. Hence, the findings reported herein (and in other observational data) may simply represent associations between "sicker" populations and increased adverse outcomes, and any causality inference should be strongly discouraged.

Previous observational studies have yielded conflicting results for the risk of stroke, in which the "J-shaped phenomenon" has not been consistently observed[8, 29, 33, 34]. However, stroke was a less frequent outcome in most analyses which, as a result, meant that many lacked statistical power to assess the relationship between BP and stroke. Moreover, in SPRINT the rates of stroke were not reduced by intensive BP lowering[9], but it should be acknowledged that stroke was a component of the primary outcome (and not the primary outcome on which sample size calculations were based), hence this trial was also underpowered to assess the effect of intensive BP lowering on stroke. Our study-population had more than 900 adjudicated stroke events (almost twice the total primary outcome events reported in SPRINT) and allows the study of the association between BP levels and stroke risk in an adequately powered fashion, and show that both higher and lower BP are associated with higher stroke rates, suggesting a "J-shaped phenomenon" in this population.

The data presented herein are the first to describe the association of mean BP with several CV outcomes in a large population of MI patients with systolic dysfunction and/or heart

failure. Importantly, these findings suggest that the association between low BP levels and worse CV outcomes may be driven by a reverse causation phenomenon (as also suggested from population-based studies[30]), hence caution is warranted when interpreting associations between BP and outcomes in observational data.

Limitations

Several limitations of this study should be acknowledged: 1) this is a post-hoc analysis of "high-risk" acute MI trial-populations in which hypertension history (although more than half of the patients were hypertensive) was not an entry criteria, hence the results presented herein cannot be extrapolated to other populations; 2) the retrospective nature of these results makes them prone to confounding and causality cannot be presumed nor even suggested; 3) despite extensive adjustment, many unmeasured variables could account for residual confounding bias; 4) the lower BP values observed near the end of life, and the lower mean BP described in patients who died from cardiovascular causes suggests a reverse causation phenomenon as responsible for the associations of low blood pressure with cardiovascular death, however this phenomenon should be highlighted and data from RCT should be preferred to observational associations; 5) patients with CV events also had a shorter follow-up which may have contributed for reverse causation to have influenced the associations described in the present manuscript; 6) BP measurements were made at the office in trial visits and did not use standardized techniques across trial and centres, however given the great number of patients and measures the occurrence of systematic error is unlikely; 7) clinical variables and outcome events were ascertained in each trial by the study investigators and independent adjudication committees, respectively. Errors in clinical records and event adjudication might have occurred, however these are also unlikely to be systematic and influence the associations presented herein in a systematic fashion; 8) medication doses or changes during follow-up are not available in the dataset, therefore we cannot ascertain which patients had treatment intensification during the trial; 9) biomarkers (e.g. NT-proBNP and Troponins) could help in better stratifying patients` risk, however biomarker data were not available in the dataset; 10) the datasets were transferred by the sponsors with no information on treatment allocation, hence the possible influence of the treatment allocation on blood pressure and outcomes cannot be assessed in the present study.

Conclusions

The results of the present study in a selected population of myocardial infarction patients with systolic dysfunction or heart failure, show that blood pressure values below 125/75 mmHg were associated with worse cardiovascular outcomes. Patients with a fatal event had fewer BP measurements and lower mean BP near the deadly event. Therefore, their mean BP was lower, suggesting that a reverse causation phenomenon accounts for the associations of low BP and CV death in this setting.

Disclosures

Dr Ferreira have received Board Membership fees from Novartis and speaker fees from Roche. Dr Rossignol has received Board Membership fees from CTMA, CVRx, Fesenius Medical care, Novartis, Relypsa, Vifor Fresenius Medical Renal Pharma and Steathpeptides. Dr Zannad has received fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; and speakers' fees from Pfizer and AstraZeneca. He and Dr Rossignol are CardioRenal co-founders. All other authors reported no relationships relevant to the contents of this paper to disclose.

Acknowledgments

The authors acknowledge Pierre Pothier for the editing of the manuscript.

Funding

None.

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